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Abstract: BACKGROUND To compare the diagnostic accuracy of PET/MR and PET/CT in patients with suspected occult primary tumors. METHODS This prospective study was approved by the institutional review board. Sequential PET/CT-MR was performed in 43 patients (22 male subjects; median age, 58 years; range, 20-86 years) referred for suspected occult primary tumors. Patients were assessed with PET/CT and PET/MR for the presence of a primary tumor, lymph node metastases, and distant metastases. Wilcoxon signed-rank test was performed to compare the diagnostic accuracy of PET/CT and PET/MR. RESULT According to the standard of reference, a primary lesion was found in 14 patients. In 16 patients, the primary lesion remained occult. In the remaining 13 patients, lesions proved to be benign. PET/MR was superior to PET/CT for primary tumor detection (sensitivity/specificity, 0.85/0.97 vs 0.69/0.73; P = 0.020) and comparable to PET/CT for the detection of lymph node metastases (sensitivity/specificity, 0.93/1.00 vs 0.93/0.93; P = 0.157) and distant metastases (sensitivity/specificity, 1.00/0.97 vs 0.82/1.00; P = 0.564). PET/CT tended to misclassify physiologic FDG uptake as malignancy compared with PET/MR (8 patients vs 1 patient). CONCLUSIONS PET/MR outperforms PET/CT in the workup of suspected occult malignancies. PET/MR may replace PET/CT to improve clinical workflow.

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PET/MR Outperforms PET/CT in Suspected Occult Tumors

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Background: To compare the diagnostic accuracy of PET/MR and PET/CT in patients with suspected occult primary tumors.

Methods: This prospective study was approved by the institutional review board. Sequential PET/CT-MR was performed in 43 patients (22 male subjects; median age, 58 years; range, 20-86 years) referred for suspected occult primary tumors. Patients were assessed with PET/CT and PET/MR for the presence of a primary tumor, lymph node metastases, and distant metastases. Wilcoxon signed-rank test was performed to compare the diagnostic accuracy of PET/CT and PET/MR.

Result: According to the standard of reference, a primary lesion was found in 14 patients. In 16 patients, the primary lesion remained occult. In the remaining 13 patients, lesions proved to be benign. PET/MR was superior to PET/CT for primary tumor detection (sensitivity/specificity, 0.85/0.97 vs 0.69/0.73; $P = 0.020$) and comparable to PET/CT for the detection of lymph node metastases (sensitivity/specificity, 0.93/1.00 vs 0.93/0.93; $P = 0.157$) and distant metastases (sensitivity/specificity, 1.00/0.97 vs 0.82/1.00; $P = 0.564$). PET/CT tended to misclassify physiologic FDG uptake as malignancy compared with PET/MR (8 patients vs 1 patient).

Conclusions: PET/MR outperforms PET/CT in the workup of suspected occult malignancies. PET/MR may replace PET/CT to improve clinical workflow.

Key Words: PET/MR, PET/CT, oncology, head and neck cancer, multimodality imaging, cancer of unknown primary, occult tumors

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Occult tumors may manifest with metastases to lymph nodes or to organs, with paraneoplastic symptoms or with increased serum tumor markers. Carcinoma of unknown primary (CUP) is defined as metastatic malignancy whose primary site cannot be detected at the time of diagnosis.[1] Carcinoma of unknown primary ranks among the top 10 of cancer diagnoses worldwide, accounting for 3% to 5% of all malignant tumors.[1,2] The frequency of CUP diagnoses heavily depends on previously performed diagnostic workup, including cross-sectional imaging. Carcinoma of unknown primary represents an inhomogeneous group of tumors.[1] Prognosis of patients is generally dismal.[1,3,4] To treat CUP patients appropriately, not only information on histopathological features and tumor markers is important but also knowledge about coexisting metastatic lesions and—most pertinent—about the presumed primary site. Treatment options vary considerably depending on primary site and extent of metastatic spread.[3] Therefore, whole-body imaging examinations are considered first choice in the evaluation of patients with suspected occult malignancies. ^{18}F-fluoro-2-deoxy-D-glucose (FDG)–PET/CT is one preferred imaging modality because of its comparably high detectability of primary sites, reaching approximately 30%.[5–8] PET/CT is reimbursed in several countries for this indication, despite absence of evidence that PET/CT is truly cost-effective.[9,10] Other options would be whole-body CT or MRI. Although there is currently no agreement on the cross-sectional imaging algorithm in the assessment of CUP patients, PET/CT was shown to be more sensitive and more effective than contrast-enhanced CT or MR.[11,12] In our experience, centers with access to PET/CT use this tool early on. It is understood that any delay in the diagnostic workflow may eventually worsen the prognosis of the patient.

The most recent hybrid imaging modality potentially suitable for CUP patients is PET/MR.[13–18] To date, the diagnostic capability of PET/MR in occult malignancies has not been studied.

The purpose of this preliminary study was to assess the diagnostic accuracy of PET/MR compared with PET/CT in patients with suspected occult malignancies.

PATIENTS AND METHODS

This prospective study was approved by the institutional review board. All subjects provided signed informed consent before enrollment. There was financial support by an institutional grant from GE Healthcare. Only non-GE employees had control of inclusion of data and information that might present a conflict of interest for those authors who are employees of GE Healthcare. Inclusion criteria were referral for PET/CT for the assessment of a suspected occult malignancy between January 2011 and August 2014 and willingness to undergo an additional MR examination. Exclusion criteria were contraindications to MRI (eg, implanted medical devices, metallic foreign bodies, severe claustrophobia). According to these criteria, we enrolled a total of 43 patients (22 male subjects; median age, 58 years; range, 20–86 years). Detailed patient characteristics are given in Table 1.

Imaging Techniques

All patients underwent PET/CT and MR using a trimodality PET/CT-MRI system (Discovery PET/CT 690 VCT, Discovery MR 750w; GE Healthcare, Waukesha, WI). Specifications of this system have been described previously.[14] Patients fasted for at least

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Compliance with Ethical Standard.

Conflicts of interest and sources of funding: P.V.-H. received IIS Grants from Bayer Healthcare, Roche Pharmaceutical, GE Healthcare, and Siemens Medical Solutions and speaker fees from GE Healthcare. G.D. is an employee of GE Healthcare. Only non-GE Healthcare employees had control of inclusion of data and information that might present a conflict of interest for authors who are employees of GE Healthcare. None declared to other authors.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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TABLE 1. Initial Patient and Tumor Characteristics

No. patients	43
Sex	
Male	22 (51%)
Female	21 (49%)
Patient age (median, range) [yr]	58 (20–86)
≥ 60	20 (47%)
< 60	23 (53%)
Initial reason for clinical diagnosis of CUP	
Malignant lymphadenopathy, verified by histopathology	
Upper cervical	17 (40%)
Mediastinal	4 (9%)
Pelvic	1 (2%)
Other solid organ findings	
Neck mass	1 (2%)
Suspected lung metastases	3 (7%)
Suspected liver metastases	4 (9%)
Suspected adrenal metastasis	1 (2%)
Retroperitoneal mass	1 (2%)
Subcutaneous mass	2 (5%)
Pelvic effusion and suspected peritoneal carcinomatosis	1 (2%)
Nonsolid findings	
Paraneoplastic symptoms	6 (14%)
Fever of unknown origin and systemic inflammation	1 (2%)
Increased serum tumor marker	1 (2%)
Initial histopathology	
Squamous cell carcinoma	17 (40%)
Adenocarcinoma	3 (7%)
Non-small cell carcinoma	1 (2%)
Poorly differentiated carcinoma	1 (2%)
Paraganglioma	1 (2%)
Mucinous carcinoma	1 (2%)
Mucoepidermoid carcinoma	1 (2%)
Not available	18 (42%)
Imaging workup before PET/CT-MR (within 4 months)	
Regional CT	16 (37%)
Regional MRI	10 (23%)
Ultrasound	26 (60%)
Endoscopy	15 (30%)
No imaging workup	3 (7%)

4 hours before the injection of a standard dose of 4.5 MBq/kg of FDG per kilogram body weight. After an uptake time of 30 minutes, patients were positioned on the shuttle table in the MR suite, and MR datasets were acquired (whole-body nonenhanced sequences, regionalized contrast-enhanced sequences covering the clinically suspected location of the primary tumor [if applicable; depending, eg, on location and histopathology of metastases]). In 19 patients, the intravenously injected amount of contrast medium (Omniscan; GE Healthcare) was 0.2 mL/kg body weight, using an injection rate of 1.5 mL/s. The other 24 patients did not receive contrast because no particular primary site was suspected clinically. After completion of the MR examination (total MR acquisition time limited to approximately 25 minutes), coils were removed without patient repositioning, and patients were transferred to the PET/CT scanner. Subsequently (at approximately 60 minutes after FDG injection), a nonenhanced CT scan and PET emission data were acquired from the mid-thigh to the vertex of the skull. In the 19 patients mentioned previously, 70 to 100 mL of iodinated contrast medium (Visipaque 320; GE Healthcare) were injected intravenously at a rate of 3 mL/s directly after the acquisition of the PET data, to acquire a regionalized contrast-enhanced CT exam.

MRI

For image acquisition, radiofrequency coils were used for the whole body (GEM 48-channel AA&PA; GE Healthcare) and for the head and neck (GEM 20-channel HNU; GE Healthcare), if applicable. MRI used several pulse sequences. Whole-body multi-section imaging was performed using an axial T1-weighted 3D dual-echo gradient-echo sequence (TR, 4.3 ms; TE, 1.3/2.6 ms; flip angle, 12 degrees; parallel imaging acceleration factor, 2; voxel size, 1.95×1.95×2.60 mm; scan time, 18 seconds per bed; 6 bed acquisition, liver accelerated volume acquisition [LAVA]-Flex; GE Healthcare), which is identical to the sequence used for attenuation correction on integrated PET/MR machines. Such a rather short MR protocol was previously shown to be diagnostically comparable to "low-dose" CT.[19] Additional regionalized MR pulse sequences were chosen based on the suspected location of the primary tumor (head and neck, chest, abdomen), if individual patient history and referral information allowed for such an assumption. In case of a suspected head and neck primary, the protocol used was published previously.[20] For a suspected thoracic primary, an axial T2-weighted sequence with motion correction (periodically rotated overlapping parallel lines with enhanced reconstruction [PROPELLER]; GE Healthcare) (TR, 9321 ms; TE, 122 ms; parallel imaging acceleration factor, 3; voxel size, 1.38×1.38×4.50 mm; scan time, approximately 5 minutes; 1 bed acquisition), acquired during free breathing, and a contrast-enhanced LAVA-Flex sequence were used. For a suspected intra-abdominal primary, the same sequences were used. All regionalized protocols took less than 20 minutes of acquisition time, fitting into the 25 minutes of total MR acquisition time during the uptake period. The rationale of this approach was to use MR sequences that could readily be implemented into a PET/MR protocol on an integrated scanner.[21]

PET/CT

All CT scans were acquired in breath-hold. The whole-body scan parameters were as follows: tube voltage of 120 to 140 kV, tube current with automated dose modulation of 30 to 60 mA/slice, collimation of 64 × 0.625, pitch of 0.984:1, rotation time of 0.5 seconds, coverage speed of 78 mm/s, FOV of 50 cm, images with transverse pixel size of 0.625, and slice thickness of 3.75 mm, reconstructed in the axial plane. For the regionalized contrast-enhanced CT scan, the following parameters were different: tube current of 60 to 440 mA/slice and image slice thickness of 1.25 mm, reconstructed in axial, coronal, and sagittal plane.

PET data were acquired in 3D time of flight (TOF) mode with a scan duration of 2 minutes per bed position, 23% overlap of bed positions, and an axial FOV of 153 mm. The emission data were corrected for attenuation using CT and were iteratively reconstructed (matrix size of 256 × 256 pixels, 3D TOF ordered subset expectation maximization with 3 iterations and 18 subsets, with point spread function, 4.7 mm full width at half maximum, 1:4:1 weighted axial filtering).

Image Evaluation

The acquired PET, CT, and MR images were transmitted to a dedicated review workstation (Advantage Workstation, Version 4.6; GE Healthcare) for the review of PET, CT, and MR images side by side or in fused/overlay mode (PET/CT; PET/MR).

Four radiologists/nuclear medicine physicians (B.-R.S., F.B., C.E.M., and M.W.H.) with 5 to 9 years of experience in PET/CT

and/or MR reading analyzed the images in random order and were blinded to all clinical data except the suspected presence and—if applicable—suspected location of the occult tumor. Readers were separated into 2 review boards. Review board A interpreted PET/CT only, and review board B interpreted PET/MR only. An intraboard consensus decision was reached if the results of the 2 readers were different. To clarify the impact of the PET component on diagnostic accuracy, and to address the performance of the anatomical imaging components, analyses of PET/CT versus CT, PET/MR versus MR, and CT versus MR were carried out additionally.

Standard of Reference

The standard of reference consisted of clinical findings in all patients including intraoperative results and histopathology, if available, and clinical and imaging follow-up (median, 1204 days; range, 523–1848 days), containing at least one cross-sectional imaging modality in each patient. If, until the end of follow-up, no primary tumor had been detected in a patient with a metastasis verified by histopathology, the patient was rated as negative for primary tumor, that is, true CUP.

One expert reader, who was not part of the review boards, finally defined presence and location of malignant and benign lesions in case histopathology was unavailable or clinical tests were inconclusive. This reader was unblinded to all patient data, including all available previous exams and follow-up exams.

Statistical Analysis

The sensitivity; specificity; positive predictive value; negative predictive value; accuracy for the detection of the primary site; and detection of lymph node metastases and distant metastases on PET/CT, PET/MR, CT, and MR were calculated. The diagnostic accuracy of each modality was assessed using McNemar test. The difference of diagnostic accuracy between PET/CT and PET/MR was addressed using Wilcoxon signed-rank test. $P < 0.05$ was deemed statistically significant. All statistical analyses used IBM SPSS Statistics 19.0.0 (IBM, Armonk, NY).

RESULTS

Forty-three patients referred for whole-body staging underwent PET/CT-MRI. The median time to imaging was 28 days (range, 6–214 days). PET/CT acquisition took 20 ± 2 minutes (mean ± SD), and MR acquisition took 21 ± 5 minutes. The mean administered dosage was 268 ± 66 MBq.

Initial patient characteristics, reasons for referral, and initial histopathology (if available) are given in Table 1. Eleven of the CUP patients with cervical lymphadenopathy had lymph node resection before inclusion into the study. Presence and location of primary tumors according to the standard of reference are given in Table 2. Thirty (69.8%) of 43 patients had malignant disease. Accuracy of PET/CT, PET/MR, CT, and MRI are given in Tables 3 and 4. Details about misdiagnoses with both modalities are given in Table 5. PET/MR was significantly superior to PET/CT in the detection of the primary site ($P = 0.020$). The same applied to MR and CT ($P = 0.011$).

TABLE 2. Final Diagnosis

Primary lesions	
Malignant (n = 30, 69.8%)	
Unknown	16 (37%)
Head and neck cancer	3 (7%)
Lung cancer	3 (7%)
Cholangiocarcinoma	2 (5%)
Liver carcinoma	1 (2%)
Appendix carcinoma	1 (2%)
Vaginal carcinoma	1 (2%)
Paraganglioma	1 (2%)
Hodgkin disease	1 (2%)
Castleman disease*	1 (2%)
Benign (n = 13, 30.2%)	
Idiopathic lymphadenopathy	4 (9%)
Sarcoidosis	2 (5%)
Viral infection	2 (5%)
Multiple sclerosis	1 (2%)
Multiple system atrophy	1 (2%)
Adrenal adenoma	1 (2%)
Inflammatory lung nodule	1 (2%)
Idiopathic tumor marker elevation	1 (2%)
Lymph node metastases (region involved, patient-based)	
Cervical	6 (14%)
Periportal	1 (2%)
Retroperitoneal	1 (2%)
Inguinal	1 (2%)
Mediastinal + hilar	3 (7%)
Cervical + mediastinal + hilar	1 (2%)
Axillary + mediastinal + hilar	1 (2%)
Cervical + axillary + mediastinal + hilar	1 (2%)
No malignant nodal disease	28 (65%)
Distant metastases (organ or site involved, patient-based)	
Lung	1 (2%)
Liver	2 (5%)
Bone	3 (7%)
Lung + liver	1 (2%)
Lung + muscle	1 (2%)
Spleen + muscle	1 (2%)
Lung + liver + muscle	1 (2%)
Retroperitoneum + bone + muscle	1 (2%)
No distant metastasis	32 (74%)

*Because Castleman disease is a lymphoproliferative disorder of unknown etiology with clinical features and treatment options similar to malignant lymphoma, it was summarized under malignant.

Primary Site

PET/CT detected a primary tumor in 9 (30%) of 30 patients with malignant disease, and PET/MR in 11 (36.7%) of 30. PET/CT readers incorrectly classified 5 sites of physiologic FDG uptake (2 larynx, nasopharynx, tonsil, and rectum) as primary site. One Tornwaldt cyst with FDG uptake was mistaken for a primary nasopharyngeal carcinoma. PET/CT also misclassified several malignant lesions: One patient with squamous cell CUP metastatic to the bone, lung, and skin was misclassified as metastasizing skin cancer. In another patient, a lung metastasis was misdiagnosed as primary lung cancer. One primary cholangiocarcinoma was mistaken for a liver metastasis. One kidney metastasis from primary lung carcinoma was mistaken for a primary renal cell carcinoma. In 1 patient, retroperitoneal Castleman disease with renal infiltration was mistaken for a primary renal cell carcinoma with retroperitoneal lymph node metastasis. In another patient, a small appendix carcinoma was missed, whereas the coexisting pseudomyxoma was mistaken for ascites of unknown etiology.

PET/MR readers incorrectly diagnosed one lung metastasis as primary bronchial carcinoma, one T1 nasopharyngeal carcinoma

TABLE 3. Diagnostic Accuracy of Each Modality for 43 Patients (Numerical Display)

		Primary Tumor	Lymph Node Metastasis	Distant Metastasis
PET/CT	TP	9	14	9
	TN	22	26	32
	FP	8	2	0
	FN	4	1	2
PET/MR	TP	11	14	11
	TN	29	28	31
	FP	1	0	1
	FN	2	1	0
CT	TP	7	13	3
	TN	23	24	30
	FP	7	4	2
	FN	6	2	8
MRI	TP	9	13	6
	TN	29	28	29
	FP	1	0	3
	FN	4	2	5

TP indicates true positive; FP, false positive; FN, false negative; TN, true negative.

as physiologic FDG uptake, and one retroperitoneal paraganglioma as lymph node metastasis from CUP.

Lymph Node Metastases

In addition to the points listed previously, both PET/CT and PET/MR readers missed one biopsy-proven inguinal lymph node metastasis due to low FDG uptake.

Distant Metastases

In addition to the results mentioned previously, PET/CT readers missed one liver metastasis due to low FDG uptake and mistook one lung metastasis for an inflammatory infiltrate. In a patient with paraneoplastic symptoms, PET/MR readers misclassified one FDG-avid pituitary adenoma as hypophysitis.

Impact of PET Component on CT and MR

The PET component added value to both CT and MRI for the correct diagnosis, particularly with regard to the sensitivity for distant metastasis (Tables 3 and 4).

Representative cases are given in Figures 1 and 2.

We grouped all 22 false positives (FP) and false negatives (FN) into 4 categories according to the reason of misdiagnosis (Table 5). Nine (40.9%) of 22 misdiagnoses were due to physiologic or benign FDG uptake, most of them were head and neck lesions (5 of 9; 55.5%). In this category, PET/MR was superior to PET/CT

TABLE 4. Diagnostic Accuracy of Each Modality for 43 Patients (Percentage Display)

		Primary Tumor	Lymph Node Metastasis	Distant Metastasis
PET/CT	Accuracy	0.72 (0.59–0.82)	0.93 (0.82–0.97)	0.95 (0.86–0.95)
	Sensitivity	0.69 (0.47–0.86)	0.93 (0.77–0.99)	0.82 (0.63–0.82)
	Specificity	0.73 (0.64–0.81)	0.93 (0.84–0.96)	1.00 (0.94–1.00)
	PPV	0.53 (0.36–0.66)	0.88 (0.72–0.93)	1.00 (0.77–1.00)
	NPV	0.85 (0.73–0.93)	0.96 (0.87–0.99)	0.94 (0.88–0.94)
	P	0.388	1.000	0.500
PET/MR	Accuracy	0.93 (0.82–0.97)	0.98 (0.88–0.98)	0.98 (0.89–0.98)
	Sensitivity	0.85 (0.66–0.91)	0.93 (0.80–0.93)	1.00 (0.82–1.00)
	Specificity	0.97 (0.89–0.99)	1.00 (0.93–1.00)	0.97 (0.91–0.97)
	PPV	0.92 (0.72–0.98)	1.00 (0.86–1.00)	0.92 (0.75–0.92)
	NPV	0.94 (0.86–0.96)	0.97 (0.90–0.97)	1.00 (0.94–1.00)
	P	1.000	1.000	1.000
CT	Accuracy	0.70 (0.57–0.81)	0.86 (0.73–0.92)	0.77 (0.69–0.83)
	Sensitivity	0.54 (0.33–0.73)	0.87 (0.76–0.91)	0.27 (0.11–0.40)
	Specificity	0.77 (0.67–0.85)	0.86 (0.76–0.91)	0.94 (0.88–0.98)
	PPV	0.50 (0.30–0.67)	0.76 (0.60–0.85)	0.60 (0.25–0.88)
	NPV	0.79 (0.70–0.88)	0.92 (0.82–0.98)	0.79 (0.74–0.83)
	P	1.000	0.687	0.109
MR	Accuracy	0.88 (0.77–0.92)	0.95 (0.85–0.95)	0.81 (0.70–0.90)
	Sensitivity	0.69 (0.50–0.76)	0.87 (0.72–0.87)	0.55 (0.32–0.70)
	Specificity	0.97 (0.89–0.99)	1.00 (0.92–1.00)	0.91 (0.83–0.96)
	PPV	0.90 (0.65–0.98)	1.00 (0.84–1.00)	0.67 (0.39–0.86)
	NPV	0.88 (0.80–0.90)	0.93 (0.86–0.93)	0.85 (0.78–0.90)
	P	0.375	0.500	0.727
PET/CT vs PET/MR	*P* (Wilcoxon)	0.020	0.157	0.564
CT vs MR		0.011	0.046	0.480
PET/CT vs CT		0.665	0.083	0.005
PET/MR vs MR		0.317	0.317	0.020

NPV indicates negative predictive value; PPV, positive predictive value. *P* values are given for comparison of either modality with standard of reference and for comparison of both modalities.

TABLE 5. Reasons for Misdiagnosis (n = 22)

Physiologic/benign FDG uptake misdiagnosed as malignant lesion (n = 9, 40.9%)		
PET/CT	8	(2 Nasopharynx, 2 larynx, oropharynx, kidney, rectum, para-aortic lymph node)
PET/MR	1	(Pituitary adenoma)
Metastatic lesion with FDG uptake misdiagnosed as primary site, or vice versa (n = 7, 31.8%)		
PET/CT	5	(Subcutaneous metastasis, lung metastasis, kidney metastasis, retroperitoneal Castleman disease, primary cholangiocarcinoma)
PET/MR	2	(Lung metastasis, primary retroperitoneal paraganglioma)
Malignant lesion missed due to subtle FDG uptake (n = 4, 18.2%)		
PET/CT	3	(Appendix carcinoma, liver metastasis, inguinal lymph node metastasis)
PET/MR	1	(Inguinal lymph node metastasis)
Malignant lesion with FDG uptake misdiagnosed as physiologic/benign (n = 2, 9.0%)		
PET/CT	1	(Lung metastasis)
PET/MR	1	(Nasopharyngeal carcinoma)

(1 FP vs 8 FP). Seven (31.8%) of 22 misdiagnoses were due to confusion of primary sites and metastases, and vice versa.

DISCUSSION

This preliminary study compared the diagnostic accuracy of PET/MR and PET/CT in patients with suspected occult malignancies. PET/MR was superior to PET/CT in the assessment of primary tumors. There was no significant difference between both modalities in the assessment of lymph node metastases and distant metastases.

This study was performed on a trimodality PET/CT-MR system consisting of 2 linked scanners. This system generates PET/CT and PET/MR datasets using identical PET data in each patient. This allows for an exact comparison of hybrid datasets, whereas comparisons might be limited when using 2 independent scanners. In general, tumor to normal tissue contrast increases in the time course after FDG injection and until significant decay occurs.[22] Also, separate scanners would use PET detectors with different sensitivity, and the comparably less accurate attenuation correction on PET/MR would impair a fair comparison of both modalities.[23–25] Therefore,

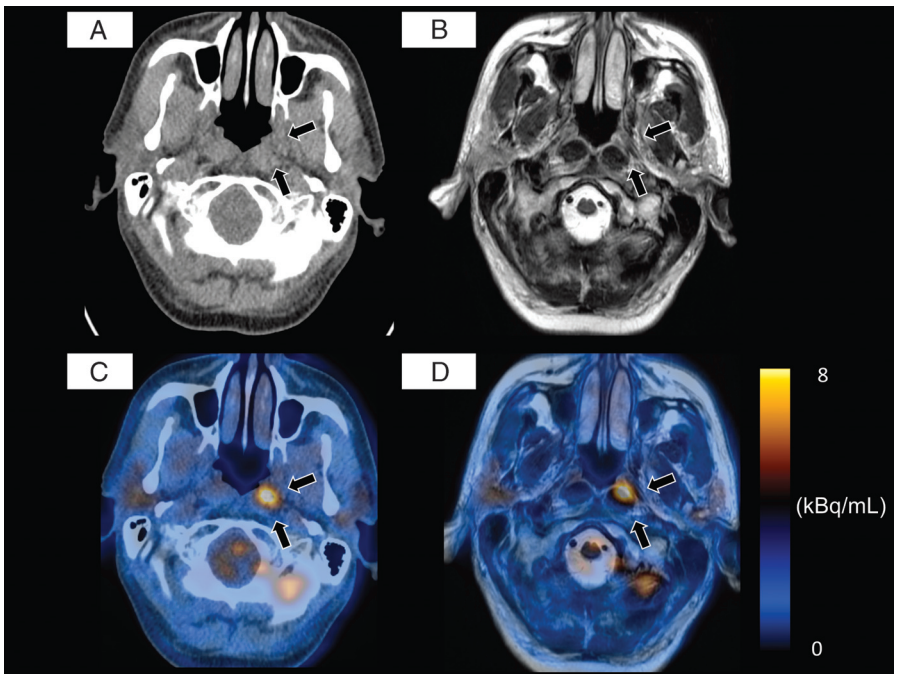

FIGURE 1. A 57-year-old woman with CUP manifesting as squamous cell carcinoma in cervical lymph nodes. CT image (**A**), T2-weighted MR image (**B**), and fused PET images corresponding to images **A** and **B** (**C** and **D**, respectively) were obtained. Fused images (**C** and **D**) show an FDG-avid lesion in the fossa of Rosenmüller (arrows), a place where occult nasopharyngeal carcinoma is sometimes located. On the CT image (**A**), no anatomical abnormality is seen (arrows); however, ruling out a tumor is difficult. On the MR image (**B**), mucosa, fat, and muscle tissue are clearly differentiated (arrows), which is helpful to assign the FDG uptake to normal tissue. After the exam, the fossa was verified to be normal by panendoscopy. Especially in the head and neck, physiologic FDG uptake may lead to false positives and may provoke unnecessary biopsy or delay of treatment. Unlike CT, MR provided complementary information for PET in this case.

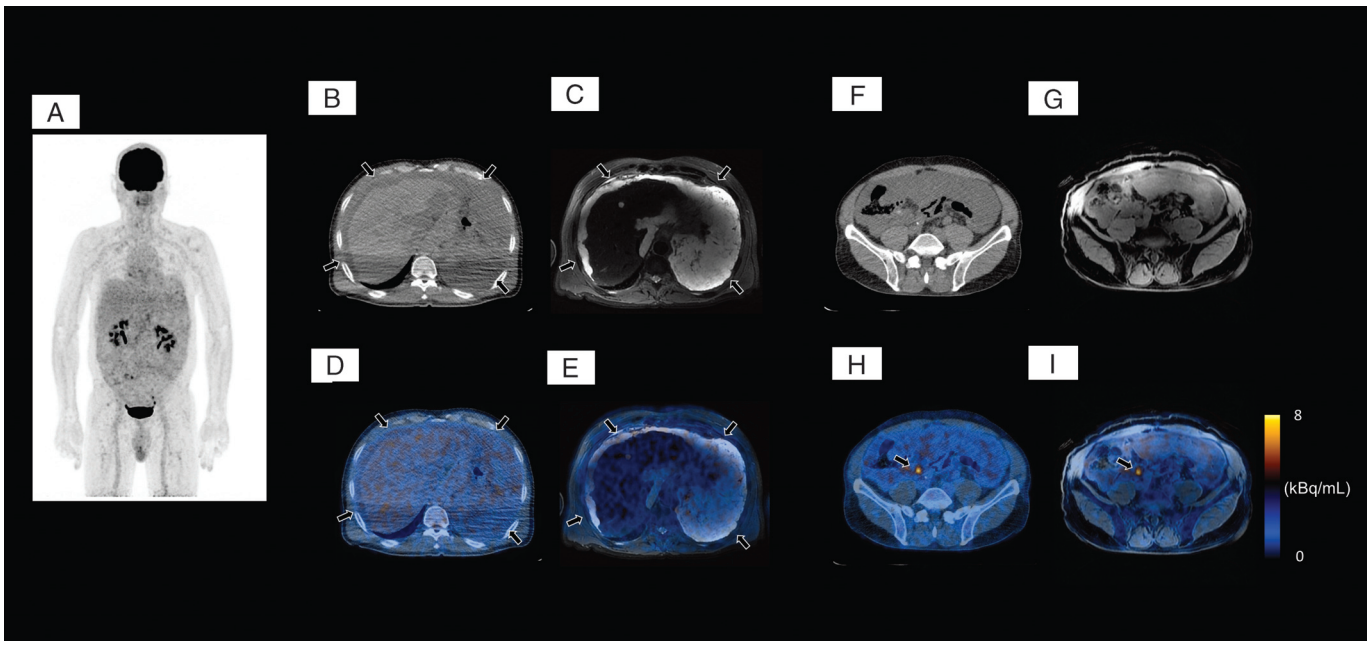

FIGURE 2. A 61-year-old woman with suspected ascites of unknown cause. Maximum intensity projection PET image (**A**), axial CT images (**B**, **F**), axial T2-weighted MR image with periodically rotated overlapping parallel lines with enhanced reconstruction method (PROPELLER) (**C**), axial T1-weighted MR image with fat suppression using the Dixon method (IDEAL) (**G**), and PET images (**D**, **H**, **E**, and **I**) corresponding to each image **B**, **F**, **C**, and **G**, respectively. Both PET with low FDG uptake and CT with homogeneous fluid density do not provide specific information for the cause of suspected ascites (arrows on **B** and **D**). On MR images, several septations are seen within the fluid, indicating loculated gelatinous ascites due to neoplastic cause rather than simple ascites (arrows on **C** and **E**). This feature, along with homogeneous hyperintensity and shear amount of the fluid, correctly suggested pseudomyxoma peritonei on PET/MR. Although the focal FDG uptake at the level of the ileocecal junction (arrow on **H**) was misinterpreted as unspecific small bowel uptake on PET/CT, PET/MR visualized the appendix and correctly suggested primary mucinous neoplasm of the appendix (**I**, arrows). Here, PET and MR provided complementary information both for the primary site and distant metastatic disease. The patient underwent right-sided hemicolectomy, and the diagnosis was verified by histopathology.

the approach used in our study eliminates several unknowns that might interfere when correlating both modalities.

In CUP patients, the most prevalent site of occult primaries is the head and neck region.[5] There, PET/CT is known to be more sensitive than contrast-enhanced CT or MRI.[11] However, physiologic uptake in normal tissue (eg, palatine tonsils, vocal cords) on PET/CT sometimes confounds image interpretation.[26,27] CT is limited in these areas because of intrinsic low soft tissue contrast. Our study indicates that MR might be more specific and be able to rule out malignancy in regions with high FDG uptake. This might help prevent unnecessary biopsy and delay of diagnosis. Five of 8 false-positive findings on PET/CT were located in the neck, whereas PET/MR was not compromised by false positives in this region. A recent study with 56 CUP patients with cervical lymph node metastases yielded a sensitivity and specificity of PET/CT of 0.69 and 0.88, respectively.[11] The discrepancy of these results to our study is likely due to differences in the patient cohort, with different previous diagnostic workup. Only 3 (17%) of 18 patients with suspected cervical CUP (17 malignant cervical lymphadenopathy and 1 neck mass) finally had a verified primary site in the head and neck in our study, compared with 32 (56%) of 57 patients in the aforementioned study. Different study designs and inhomogeneous patient samples, partly because of the inhomogeneous nature of the study subject itself, are an inherent problem for comparing diagnostic accuracies. Thus, one meta-analysis of 16 studies reported a great variation of the performance of FDG-PET (sensitivity, 0.33–1.00; specificity, 0.40–1.00).[28]

Our results are also interesting from another point of view. One recent study showed that combined contrast-enhanced CT and MRI was not superior to contrast-enhanced CT alone in CUP patients, whereas PET/CT performed better than both CT-MR and CT.[11] This is in line with our results. Our study shows that PET/MR is also superior to MR alone. Additionally, our study indicates that MR might be a better complementary anatomical imaging modality in combination with PET than CT. Besides, we found that the addition of PET enhances the performance of both CT and MR in detecting distant metastases but not in detecting primary tumors and lymph node metastases. On the other hand, MR was superior to CT only in the detection of primary tumors. These results are in line with previously published work on CUP.[2,5,11,29]

A meta-analysis of 433 CUP patients found a primary tumor detection rate of 37% with PET/CT, which is comparable to our study.[5] However, the sensitivity/specificity of PET/CT in our study was slightly inferior to this meta-analysis (0.69/0.73 vs 0.84/0.84).

In our cohort, there were 4 patients with malignant lung lesions. Three of them were correctly diagnosed with PET/CT and two with PET/MR. Although there was no critical disadvantage of PET/MR in the detection of lung lesions in our study, an accurate assessment of lung malignancies represents one big challenge for PET/MR in general.[30] One possible solution currently available

is special MR sequences for the lung (eg, ultra-short TE sequences, respiratory-gated T2-weighted sequences).[14,31] However, such special sequences require additional scanning time (approximately 5 minutes). In a clinical setup, the total scan time is usually limited, both as a matter of patient convenience and patient throughput.

Several studies evaluated the natural history and clinical impact of lung lesions missed on PET/MR. Roy et al evaluated the outcome of 89 non-FDG-avid lung nodules missed on PET/MR in 43 oncological patients.[32] Only 3 of 89 nodules in only 1 patient progressed, whereas the rest resolved or remained stable during 3 years of follow-up. Hence, the vast majority of non FDG-avid lung nodules is probably clinically irrelevant. Although further studies are needed, the clinical drawback of PET/MR in the lung might be less critical than expected.

PET/MR might improve the clinical workflow by replacing PET/CT and MRI in CUP patients. CT imaging might ensue if needed. This approach might minimize a delay of imaging examination that is known to worsen the outcome in patients with advanced malignancies such as CUP. Although the clinical workflow was not a goal of our study, our results seem to justify that PET/MR might replace PET/CT in patients with suspected occult malignancies.

Limitations

A first limitation of our study is that histopathological or surgical verification was not available for all lesions, for ethical reasons. This represents an intrinsic limitation because surgery is often precluded in metastasized tumors. Second, our study sample is too small to provide further subanalysis of body regions. Third, the acquired MR sequences were inhomogeneous. Sequences were selected depending on suspected locations of primary tumors, if possible, only being limited by the PET acquisition time, and thus matching the PET/CT acquisition time to allow for a fair comparison. All such dedicated sequences were conventional ones and did not include advanced MR techniques such as diffusion-weighted imaging with specialized technique (eg, reduced volume excitation, segmented readout) or MR perfusion. If the choice of regionalized sequences is improved in the future, the diagnostic accuracy of PET/MR in this situation is expected to be at least comparable to our study. Fourth, MR using several pulse sequences was compared with CT. However, contrast was administered for both MR and CT in the same patients, and MR acquisition time fairly matched PET/CT acquisition time. Fifth, previously performed clinical and imaging examinations represent some sort of inclusion bias for our study, which, however, cannot be avoided in patients with occult malignancies. The same bias existed for both PET/CT and PET/MR and thus does not impact on a comparison of both modalities. Sixth, approximately half of examinations were without contrast. However, previous studies revealed that the administration of contrast does not increase the accuracy of PET/CT in CUP patients.[5] Seventh, the studied population has a potential selection bias concerning the location of malignant lesions. In almost half of the patients, lesions were located in body regions where MR is supposedly superior to CT, for example, the head and neck. However, this would represent an intrinsic bias because the head and neck is the most common origin of CUP.[33] Notably, several studies have also shown equality of MR and CT in head and neck tumors.[11,34,35]

In conclusion, PET/MR outperforms PET/CT in the workup of patients with suspected occult malignancies, especially in those with cervical disease. PET/MR was comparable to PET/CT in detecting lymph node metastases and distant metastases. Our study indicates that PET/MR might replace PET/CT in CUP patients to improve clinical workflow.

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